

Management of Refractory Variceal Bleed in Cirrhosis



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Acute variceal bleeding is the major cause of mortality in patients with cirrhosis. The standard medical and endoscopic treatment has reduced the mortality of variceal bleeding from 50% to 10–20%. The refractory variceal bleed is either because of failure to control the bleed or failure of secondary prophylaxis. The patients refractory to standard medical therapy need further interventions. The rescue therapies include balloon tamponade, self-expanding metal stents (SEMS) placement, shunt procedures, including transjugular intrahepatic portosystemic shunt (TIPS), balloon-occluded retrograde transvenous obliteration (BRTO), and endoscopic ultrasound (EUS) guided coiling.

In cases where endoscopic variceal ligation (EVL) has failed and the variceal bleeding continues, temporary measures like balloon tamponade can be used to achieve hemostasis and as a bridge to definitive measures. SEMS being in use for refractory bleed is preferred over balloon tamponade due to the reduced complication rate. The shunting procedures are highly effective in reducing portal pressure and represent the gold standard for uncontrolled variceal bleeding. The surgical shunts, as well as nonshunt surgeries such as devascularization have become less popular with the increasing use of minimally invasive techniques like TIPS. TIPS have high success rates in controlling refractory variceal bleeding. The mortality rate is greater in high-risk patients undergoing salvage TIPS, and hence, pre-emptive TIPS should be considered in these patients. BRTO is an interventional radiologic procedure used in the management of bleeding gastric and ectopic varices. The availability of gastroduodenal or splenorenal shunts is required for the BRTO procedure, which helps to reach and obliterate the cardiofundal varices through the femoral or jugular vein approach. The EUS guided coiling and glue injection have shown promising results, and further randomized controlled trials are required to establish their efficacy for refractory variceal bleeding. (J CLIN EXP HEPATOL 2022;12:595–602)

Liver disease is one of the leading causes of morbidity and mortality worldwide being responsible for 1.2% of all patients attending the hospitals as per a recent Indian multicenter study.¹ One of the major causes of mortality in these cirrhotic patients is acute variceal bleeding.² The mortality rate is higher in patients with the severe disease, with up to 30% in patients with Child-Pugh C dying in contrast to much lower in those with Child-Pugh A liver cirrhosis.³

Portal hypertension in liver cirrhosis is responsible for the development of gastrointestinal varices. The varices are usually present in patients with hepatic venous pressure gradient (HVPG) >10 mmHg and those having

HVPG >12 mmHg are at a higher risk of variceal bleeding. Bleeding risk is significantly reduced when the HVPG is reduced by $\geq 20\%$ or to ≤ 12 mm Hg, and the mortality is also reduced with a decrease of $\geq 20\%$ in HVPG.⁴

The standard management of variceal bleeding includes hemodynamic stabilization, prophylactic antibiotics, vasoactive agents like terlipressin, somatostatin, and its analogs and endoscopic treatment. Endoscopic variceal ligation (EVL) and injection sclerotherapy are standard endoscopic therapy performed after the initial stabilization of the patient. EVL is presently the preferred initial therapy because of higher success rate and lowers adverse effect compared to sclerotherapy. For gastric varices, the preferred initial modality of treatment is glue or thrombin injection. The standard medical and endoscopic treatment has reduced the mortality in patients with variceal bleeding from 50 to 10–20%.⁵ The patients, refractory to standard medical therapy, need further interventions.

DEFINITIONS

The refractory variceal bleed is either because of failure to control the bleed or failure of secondary prophylaxis. The previous Baveno consensus has defined failure to control variceal bleeding, which was modified in the Baveno V consensus.^{6–10} Baveno VI consensus has used the same definition as Baveno 5 for treatment failure.¹¹ Treatment

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Abbreviations: BAATO: balloon-assisted antegrade transvenous obliteration; BRTO: balloonoccluded retrograde transvenous obliteration; DIPS: direct intrahepatic portacaval shunt; EUS: endoscopic ultrasound; EVL: endoscopic variceal ligation; HVPG: hepatic venous pressure gradient; PARTO: plug-assisted retrograde transvenous obliteration; PTFE: polytetrafluoroethylene; PVT: portal vein thrombosis; TIPS: transjugular intrahepatic portosystemic shunt

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failure is considered as the inability to control bleeding within the first 5 days and demands for a change in treatment as per the criteria mentioned in Table 1.^{12,13}

If the acute bleeding episode continues despite the initial treatment and the patient is hemodynamically stable, a second endoscopic attempt may be useful. This holds true, especially if the initial attempt was not made under ideal circumstances or the procedure was performed by an inexperienced endoscopist. If the bleeding is severe or the patient is hemodynamically unstable, rescue therapies discussed below should be used. The rescue therapies include balloon tamponade, self-expanding metal stents (SEMS) placement, shunt procedures, including transjugular intrahepatic portosystemic shunt (TIPS), balloon-occluded retrograde transvenous obliteration (BRTO), and endoscopic ultrasound (EUS) guided coiling.

Balloon Tamponade

In cases where EVL has failed and the variceal bleeding continues, temporary measures like balloon tamponade should be used to achieve hemostasis and as a bridge to definitive measures, such as TIPS or variceal shunt surgery. The superficial, submucosal vessels and thin walls of the varices make them ideal for compression by balloon tamponade. The Sengstaken-Blakemore tube (Figure 1a)¹⁴ has three ports for gastric balloon inflation (200–400 ml), esophageal balloon inflation, and gastric aspiration.¹⁵ While using the Sengstaken-Blakemore tube, one should first inflate the gastric balloon up to 100 ml and confirm its position on X-ray. After confirming position, the gastric balloon can be inflated up to 400 ml and then pulled up till the gastroesophageal junction resistance is felt. The esophageal balloon is only inflated if bleeding continues despite inflation of the gastric balloon.

The Minnesota tube (Figure 1b)¹⁴ is a modification of the Sengstaken-Blakemore tube (Figure 1c)¹⁴ that has a larger gastric balloon (up to 500 ml) and a fourth port for esophageal aspiration. The Linton-Nachlas tube has no esophageal balloon for inflation but has a larger gastric balloon (up to 600 ml) and is found to be more effective in fundal variceal bleeding.¹⁶ The characteristics of all three balloons have been compared in Table 2.

The success rate for achieving hemostasis in variceal bleeding was 91.5%, with the Sengstaken-Blakemore used for esophageal varices and was 88% for those treated with the Linton-Nachlas tube for gastric variceal bleeding.¹⁷ The balloon tamponade is usually not kept for more than 24 h due to the risk of major complications. The adverse events are more frequently seen in series where the tubes were inserted by inexperienced staff.¹⁸ Adverse events include aspiration, pressure necrosis, nasal cartilage damage and are known to occur in 6–20% of patients.¹⁹ The most lethal complication is esophageal rupture (Figure 2).

Self-expanding Metal Stents

Endoscopically placed SEMS work by compressing varices after expansion in the lower esophagus are an alternative treatment to balloon tamponade for temporary hemostasis. They can be placed in the esophagus for up to 2 weeks and have a lower rate of complications and blood transfusion requirements when compared with balloon tamponade.^{20,21} Migration of the stent (28%), rebleeding after stent removal (16%), and esophageal ulcerations are, however, the known complications.^{22,23}

In a systematic review and meta-analysis incorporating 155 patients of refractory variceal bleeding from 12 studies, the pooled clinical and technical success rate of SEMS in controlling the variceal bleed was 96% (95% CI: 0.90–1.00) and 97%, respectively (95% CI: 0.91–1.00).²⁴ The different types of SEMS included in this study were the Choo stent, Ella-Boubela-Danis stent, and the SX-Ella Danis stent (Ella-CS, Hradec Kralove, Czech Republic). The SX-Ella Danis stent (Figure 3) is a dedicated, covered, removable SEMS used for esophageal variceal bleeding, which can be easily deployed and removed at endoscopy. The stent is often placed under fluoroscopic guidance, but in an emergency situation, the procedure can be performed at the bedside without any fluoroscopic guidance. The stent has two radiopaque markers at both ends and at midpoints that help to assess the expansion and position of the stent on a chest X-ray. Experience at our center with SX-ELLA Danis stent for difficult variceal bleeding has shown successful

Table 1 Definitions for Refractory Variceal Bleed.

Failure to Control Bleeding	Failure of Secondary Prophylaxis
• Acute variceal bleeding <5 days • Death or need to modify treatment due to one of the following criteria^{12,13}: 1. Fresh bleeding in the form of hematemesis or nasogastric aspiration of ≥ 100 ml after 2 h of starting medical treatment or after endoscopic intervention 2. Development of hypovolaemic shock 3. Decrease in hemoglobin of 3 g or decrease in hematocrit of 9% during any period of 24 h if no blood transfusion is done	• One episode of rebleeding after 5 days from a portal hypertensive source, which is clinically significant • Re-bleeding in the form of recurrent melena or hematemesis is clinically significant if any one of the following is present: 1. Requires hospital admission 2. Needs blood transfusion 3. Decrease in hemoglobin of 3 g 4. Death in a period of 6 weeks

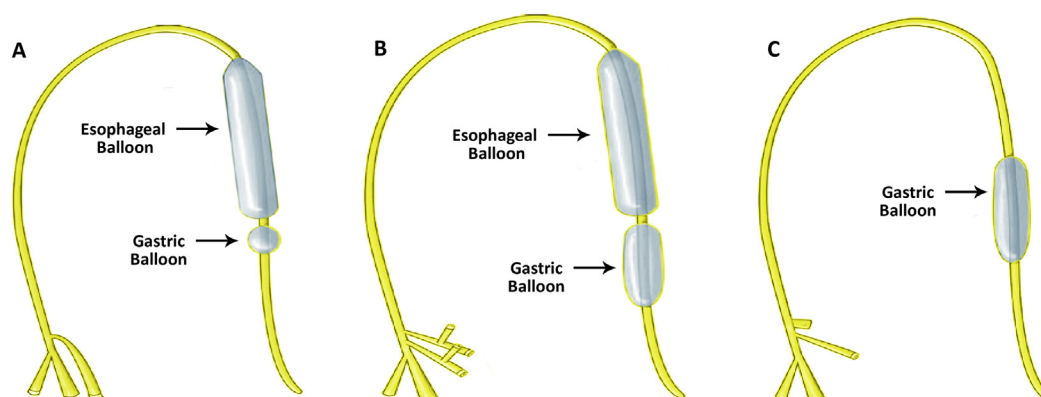


Figure 1 (a) The Sengstaken-Blakemore tube (b) The Minnesota tube (c) The Linton-Nachlas tube. Adapted and modified from Lee BT et al 2018.¹⁴

deployment and immediate technical success in all patients. Re-bleeding was seen in one of the patients, and the mean duration of stent removal was 17.5 days.²⁵ Figure 4 shows an SX-ELLA Danis stent placed in the esophagus for refractory variceal bleed.

A multicenter randomized control trial has compared the esophageal balloon tamponade (Sengstaken-Blakemore tube) with esophageal stents (SX-ELLA Danis stent) for the control of acute refractory variceal bleeding.²¹ The success with esophageal stents was 66%, while it was only 25% in the balloon tamponade group ($P = 0.025$). The transfusion requirements and adverse events were also less in the esophageal stenting group. However, the 6-week survival showed no significant difference between the two groups. The results of this study favor the use of esophageal stents over the esophageal balloon tamponade in patients with refractory esophageal variceal bleeding. SEMs, however, are more costly compared to Sengstaken-Blakemore tubes and are of no use if the bleeding is from gastric varices. The advantages and disadvantages of SEMs compared with balloon tamponade are summarized in Table 3.

Shunting Procedures

Once the patient is stabilized with the temporary hemostatic measures as discussed above, a definitive procedure should be performed. The shunting procedures are highly effective in reducing portal pressure and represent the gold standard for uncontrolled variceal bleeding.

Table 2 Characteristics of the Different Tubes Used for Balloon Tamponade in Variceal Bleeding.

Balloon	Esophageal Balloon Port	Esophageal Aspiration Port	Gastric Balloon Port	Gastric Aspiration Port
Sengstaken-Blakemore tube	Yes	No	Yes	Yes
Minnesota tube	Yes	Yes	Yes	Yes
Linton-Nachlas tube	No	Yes	Yes	Yes

Transjugular Intrahepatic Portosystemic Shunt

TIPS involves the creation of a radiological shunt with a stent/graft that directs the portal blood flow directly into the hepatic vein bypassing the liver (Figure 5). The stent of appropriate length is placed under fluoroscopic guidance between the hepatic vein and portal vein. This leads to a decrease in portal pressure, and hence, reduces portal hypertension. At times, this may also lead to hypoperfusion of liver parenchyma and result in deranged liver functions and hepatic encephalopathy. The polytetrafluoroethylene (PTFE) covered metal stents are preferred as they have improved patency and reduced chances of hepatic encephalopathy when compared to the uncovered stents.²⁶ In patients with occluded hepatic veins, a modified TIPS procedure known as direct intrahepatic portacaval shunt (DIPS) can be done. DIPS involves ultrasound-guided direct puncture of the portal vein through the inferior vena cava and the caudate lobe of the liver.

The recent British Society of Gastroenterology (BSG) guidelines recommend TIPS in refractory gastroesophageal variceal bleeding where endoscopic and medical therapy have failed.²⁷ Salvage TIPS should, however, be avoided in patients with a Child-Pugh score of more than 13. The mortality rate at 6 weeks and 12 weeks was 36% and 42% in patients undergoing salvage TIPS for refractory variceal bleeding in a recent study.²⁸ Early TIPS (pre-emptive TIPS) may be considered within 72 h of gastroesophageal variceal bleed in hemodynamically stable high-risk patients who have Child C status or MELD score ≥ 19 .²⁷ TIPS should be considered for secondary prophylaxis of gastroesophageal variceal bleeding in selected patients only. Monescillo et al, demonstrated that the use of TIPS in patients with hepatic venous pressure gradient (HVPG) > 20 mm Hg have reduced the risk of treatment failure with better survival rates.²⁹ In a recent multicenter study, the combination of MELD score and lactate was used to predict the 6-week mortality in patients undergoing salvage TIPS. The 6-week mortality was more than 90% in patients with serum lactate of ≥ 12 mmol/L and/or MELD score of ≥ 30 .³⁰

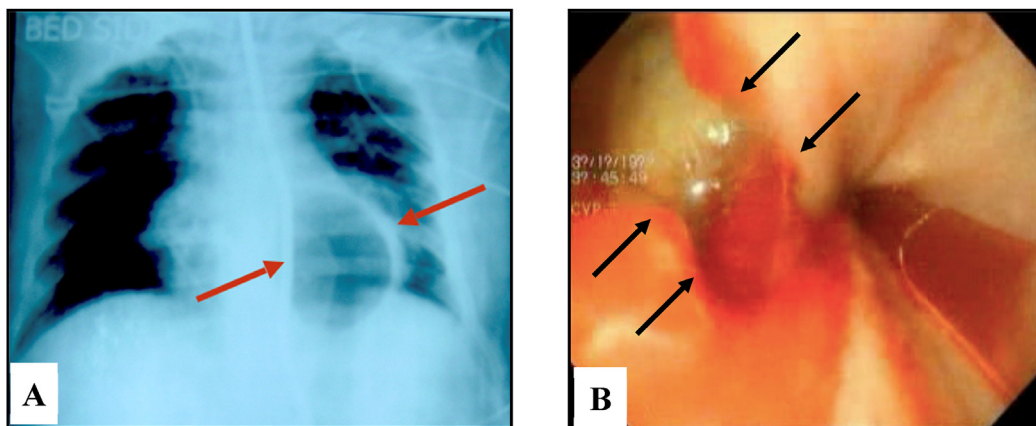


Figure 2 (A) Chest X-ray showing gastric balloon inflated in the esophagus inadvertently (B) Esophageal perforation seen on endoscopy due to inflation of the gastric balloon in the esophagus.

Intensive care unit stay prior to TIPS procedure has shown to be an independent predictor of TIPS failure and mortality at 6 weeks and 12 months in patients undergoing salvage TIPS for refractory variceal bleeding.²⁸ The complications of TIPS can be either stent-related or procedure-related. The stent-related complications are stent migration, early shunt occlusion, and hepatic encephalopathy. The procedure-related complications are fever, hemobilia, inadvertent carotid artery puncture, right atrial perforation, hepatic capsular laceration, hernia incarceration, and nontarget stent insertion. These complications are, however, rare in experienced hands.

Surgical Shunts

The surgical shunts, as well as nonshunt surgeries such as devascularisation have become less popular with the increasing use of minimally invasive techniques like TIPS. The surgical shunts are often considered as a last

resort when all other treatment options have failed. In the pediatric population, surgical shunts are performed for uncontrolled bleeding in cases with noncirrhotic portal hypertension and portal vein thrombosis.³¹ The surgical shunts can be selective (decompresses only the gastroesophageal varices, maintain portal pressure and preserve some portal flow to the liver) or nonselective (decompresses the entire portal system and all of the portal flow bypasses the liver).

The distal splenorenal shunt (Warren shunt) is the preferred selective shunt as it only decompresses the varices at the gastroesophageal junction and spleen. The variceal bleeding can be controlled with this shunt in up to 90% of patients with lesser chances of hepatic encephalopathy.³² However, the risk of ascites persists as the portal pressure in the superior mesenteric vein and portal vein remains high. The end-to-side and side-to-side portocaval shunts are nonselective surgical shunts, which result in total

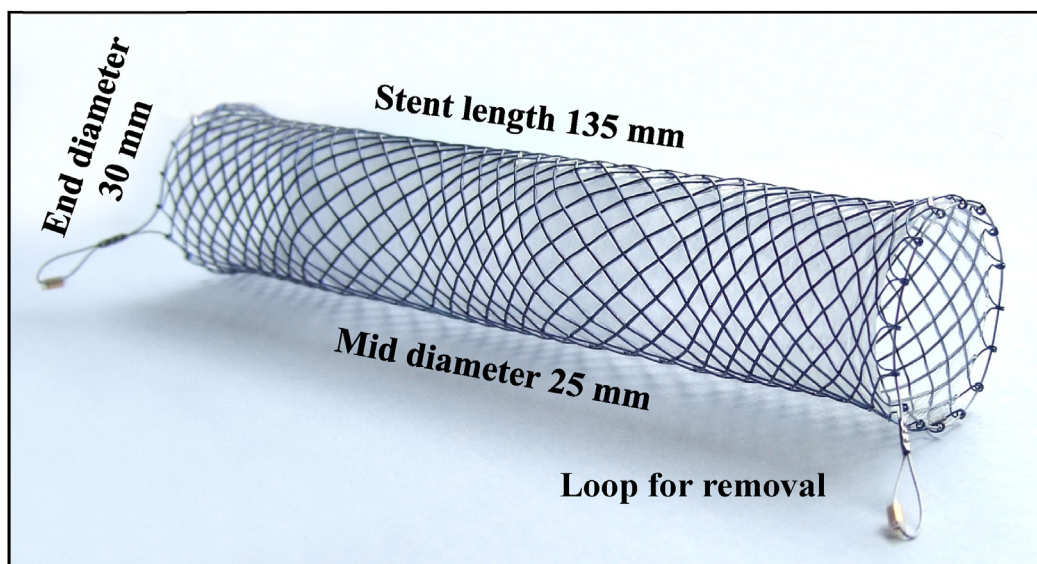


Figure 3 SX-Ella Danis stent (Ella-CS, Hradec Kralove, Czech Republic).

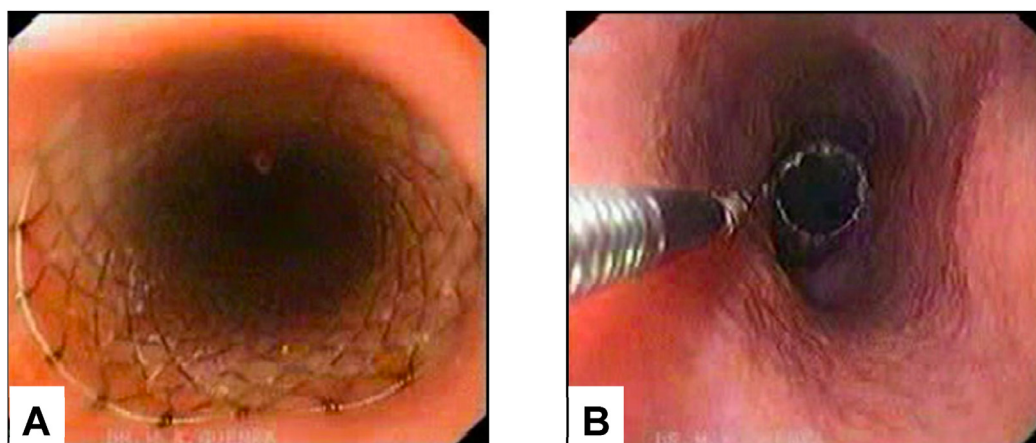


Figure 4 (A) Proximal end of Sx-Ella Danis stent seen after deployment (B) Stent being removed by pulling the proximal extractor loop. Adapted from Goenka MK et al, Indian J Gastroenterol 2017.

shunting of portal blood flow when the shunt diameter is more than 12 mm. In a randomized control trial, it was seen that portocaval shunt surgery has better bleeding control, longer survival, and lesser chances of encephalopathy when compared with emergency TIPS procedures.³³ However, more evidence is needed before using portocaval shunt surgery as a rescue procedure after the failure of initial treatment.

Balloon-occluded Retrograde Transvenous Obliteration

BRTO is an interventional radiologic procedure used in the management of bleeding gastric and ectopic varices.³⁴ Thrombosis and obliteration of the varices is induced by injecting sclerosing agents like ethanolamine oleate in the gastric varices with the retrograde balloon placement occluding the variceal blood flow. The prerequisite for the BRTO procedure is the presence of gastrorenal or splenorenal shunts. The availability of these

shunts helps to reach and obliterate the cardiofundal varices through the femoral or jugular vein approach.

The clinical success rate for the obliteration of gastric varices by BRTO was 97.3% in a systematic review and meta-analysis.³⁵ The recurrence rate of esophageal varices was 33.3%. BRTO has the potential to increase the portal blood flow, which is an advantage over other techniques, and hence, it may also be performed in patients with deranged liver functions and altered sensorium. However, the increase in portal flow may sometimes lead to aggravation of portal hypertension. Plug-assisted retrograde transvenous obliteration (PARTO), a recent modification of the BRTO, has used vascular plugs/coils and gelatine sponge instead of the sclerosant and balloon occlusion catheter to minimize the procedure-related complications.³⁶ In a recent comparison of BRTO vs TIPS, it was seen that the rebleeding rate was much less in the BRTO group (8.6%) as compared to the TIPS group (19.8%) during follow up of one year.³⁷ The mortality rate was, however, similar among both the group. The BRTO and TIPS procedure have been compared in Table 4.

In a retrospective audit of patients who underwent BRTO, it was seen that the presence of TIPS (BRTO + TIPS) reduced the chances of development of ascites and recurrent bleed post-BRTO as compared to patients who only underwent BRTO procedure. However, there was no survival benefit among the two groups.³⁸ Balloon-assisted antegrade transvenous obliteration (BAATO) combined with TIPS has also been shown to be safe and effective in the management of gastric varices in a recent study.³⁹

EUS Guided Procedure

The EUS has recently emerged as a promising option in the management of gastric varices.⁴⁰ EUS guided fine needle injection should be the preferred option to prevent recurrent gastric variceal hemorrhage.⁴¹ In a recent comparative

Table 3 Advantages and Disadvantages of SEMS Compared With Balloon Tamponade for Management of Refractory Variceal Bleed.

SEMS	Balloon tamponade
• Can be used up to 7 days	• Not more than 24 h
• Comfortable to the patient	• Uncomfortable to patient
• Allows endoscopy and oral feeding	• Endoscopy and oral feeding not possible
• Safer due to lesser chances of aspiration, esophageal perforation & other adverse events	• More chances of adverse events
• Costly	• Cheaper

SEMS: Self Expanding Metal Stent.

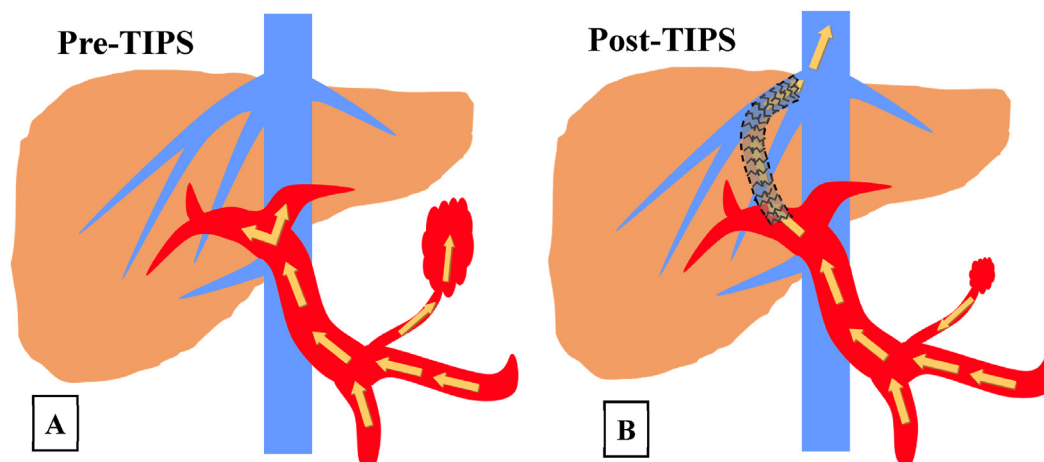


Figure 5 (A) Pre-TIPS blood diverted to the collateral circulation due to portal hypertension (B) Post-TIPS blood shunted to IVC decompressing the collateral flow. TIPS – Transjugular Intrahepatic Portosystemic Shunt; IVC- Inferior Vena Cava.

study for gastric variceal endotherapy, EUS-guided glue injection showed decreased rebleeding rate and less glue requirement in the EUS group compared to direct endoscopic glue injection. There was no significant difference in the adverse events among both groups.⁴²

The metal coils have been used in multiple studies for hemostasis of gastric variceal bleeding. The material of the coils constitutes synthetic stainless-steel fibers that slow down the vascular blood flow and promote clot formation and thrombosis of the varix. The hemostasis rate was found to be similar when EUS guided coiling was compared with glue injection, although the lesser number of endoscopies and adverse events favor the use of EUS guided coiling over glue injection.⁴² When both the modalities of coiling and glue injection were combined, the recurrence rate, average number of coils and volume of glue required was lower when compared to either of the modality alone.⁴³ In a recent meta-analysis, the combination of coil embolization and glue injection under EUS guidance was the preferred modality of treatment for gastric varices over EUS guided monotherapy.⁴⁴

In a retrospective analysis from India, Mukkada et al have shown that EUS guided coiling with or without glue injection is useful for obliterating the gastric varices in patients with rebleeding of gastric varices after glue injection.⁴⁵ Contrast-enhanced EUS gives a better evaluation of the vasculature, and this real-time imaging helps in targeting the perforators. In a recent case series, the contrast-enhanced EUS has shown to be effective and safe in injecting glue and coils by targeting the perforating feeders in gastric or ectopic varices.⁴⁶

The mortality rate from variceal bleeding remains high despite standard medical and endoscopic management.

Table 4 Comparison of BRTO and TIPS Procedure.

TIPS	BRTO
- For esophageal varices and ascites - Hepatic vein should be patent - Worsens hepatic encephalopathy - PVT is a relative contraindication - Reduces portal hypertension	- For gastric varices - Gastrorenal/lienorenal shunts are required - Does not worsen hepatic encephalopathy - Can be done in patients with PVT - Portal hypertension may be aggravated

TIPS: Transjugular Intrahepatic Portosystemic Shunt, BRTO: Balloon-occluded Retrograde Transvenous Obliteration, PVT: Portal Vein Thrombosis.

The mortality rate is decreased when the HVPBG is reduced by $\geq 20\%$. Balloon tamponade and SEMS placement are temporary measures and used as a bridge to definitive measures. The shunting procedures are highly effective in reducing the portal pressure and represent the gold standard for uncontrolled variceal bleeding. Surgical shunt procedures are more invasive and have become less popular with the increasing use of TIPS. TIPS have high success rates in controlling refractory variceal bleeding and is minimally invasive. The EUS-guided coiling and glue injection have shown promising results for the treatment of gastric variceal bleeding. The combination has shown to be superior to EUS guided monotherapy for treatment of gastric varices in recent studies. Further randomized controlled trials are required to establish its efficacy for refractory variceal bleeding. Figure 6 shows a possible management approach for acute variceal bleeding.

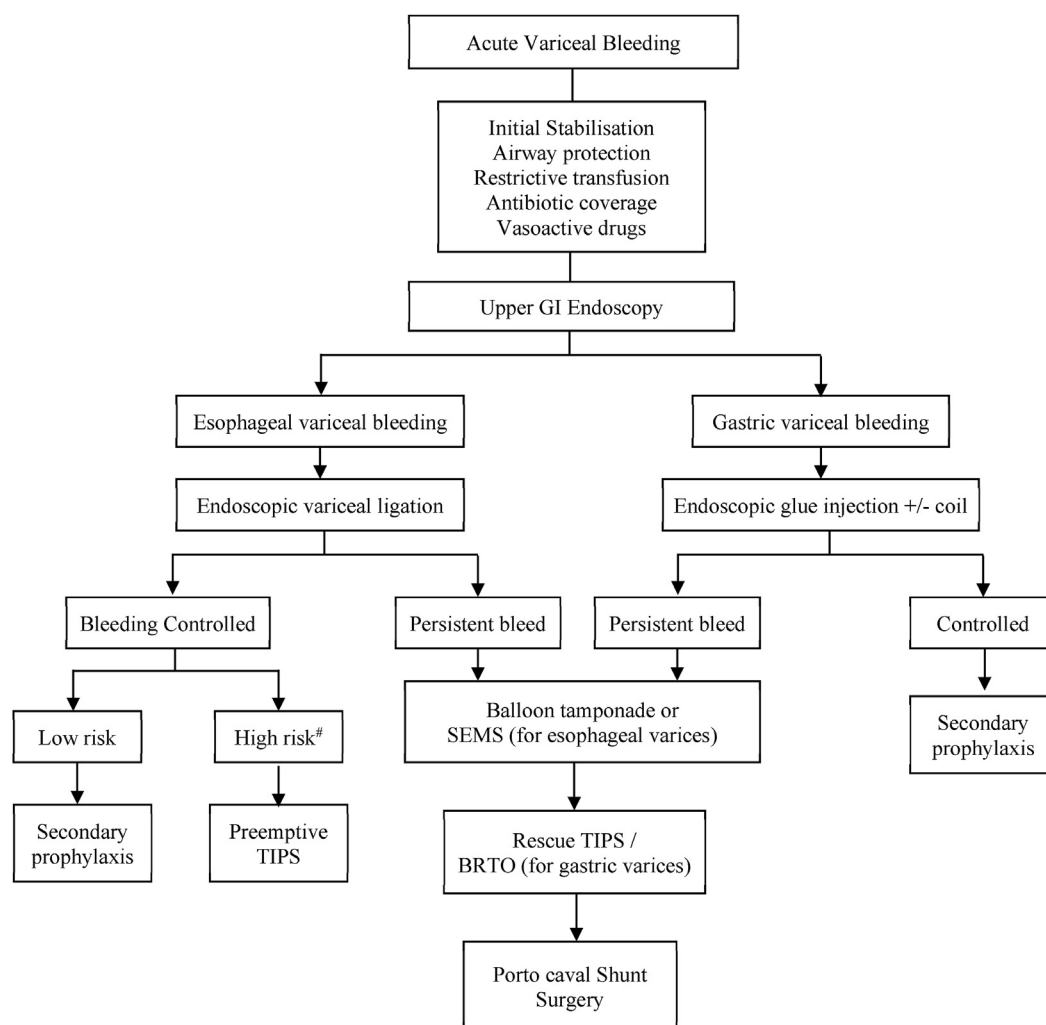


Figure 6 Approach to management for acute variceal bleeding. # – MELD score ≥ 19 or Child C. SEMS - Self-expanding metal stents; TIPS - trans-jugular intrahepatic portosystemic shunt; BRTO - balloon occluded retrograde transvenous obliteration.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Gajanan Rodge: Data curation, Writing – original draft, Investigation, Images, Software; **Usha Goenka:** Visualization, Supervision, Investigation, Images, Software; **Ma-hesh Goenka:** Conceptualization, Methodology, Supervision, Investigation, Images, Software.

CONFLICTS OF INTEREST

The authors have none to declare.

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